STN-Structure Seasch 3/13/07

10/522,321

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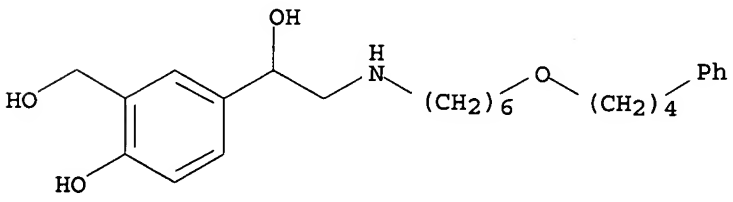
L8 ANSWER 1 OF 255 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2007:92806 CAPLUS
DOCUMENT NUMBER: 146:134517
TITLE: Validation and application of a screening method for .beta.2-agonists, anti-estrogenic substances and mesocarb in human urine using liquid chromatography/tandem mass spectrometry
AUTHOR(S): Kang, Min-Jung; Hwang, Yong Hee; Lee, Won; Kim, Dong-Hyun
CORPORATE SOURCE: Bioanalysis & Biotransformation Center, Korea Institute of Science and Technology, Seoul, 130-650, S. Korea
SOURCE: Rapid Communications in Mass Spectrometry (2007), 21(2), 252-264
CODEN: RCMSEF; ISSN: 0951-4198
PUBLISHER: John Wiley & Sons Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

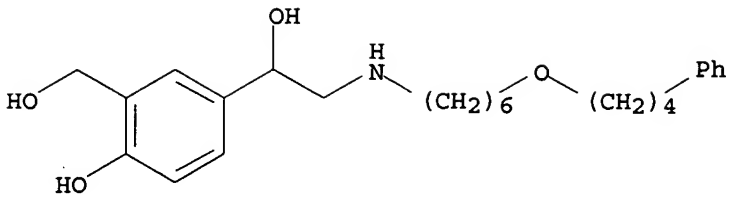
AB Electrospray ionization (ESI) mass spectra of 15 anti-estrogenic substances, .beta.2-agonists and mesocarb were investigated in terms of fragmentation patterns. On the basis of this product ion information, a simultaneous screening method for anti-estrogenic substances, .beta.2-agonists and mesocarb was developed for doping control purposes. After hydrolysis, liquid-liquid extraction was adopted for the sample preparation The recoveries for all compds. were 30 and 96%. A single liquid chromatog./tandem mass spectrometry (LC/MS/MS) anal. could be performed in 13 min for the anal. of 15 anti-estrogenic substances, .beta.2-agonists and mesocarb. A quant. anal. was also validated. Inaccuracies were below ±12% and precisions varied from 0 to 15.8%. The limit of detection was below 10 ng/mL except formestane (300 ng/mL) and aminoglutethimide (100 ng/mL). The validated method was applied for the anal. of excretion samples.

IT 89365-50-4, Salmeterol
RL: ANT (Analyte); ANST (Analytical study)
(β 2-agonists, antiestrogens, and mesocarb in human urine determined by HPLC-ESI-MS-MS)
RN 89365-50-4 CAPLUS
CN 1,3-Benzenedimethanol, 4-hydroxy-α1-[[[6-(4-phenylbutoxy)hexyl]amino]methyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 2 OF 255 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2007:75445 CAPLUS
DOCUMENT NUMBER: 146:198297
TITLE: Improved outcomes in patients with chronic obstructive pulmonary disease treated with salmeterol compared with placebo/usual therapy: results of a meta-analysis



REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

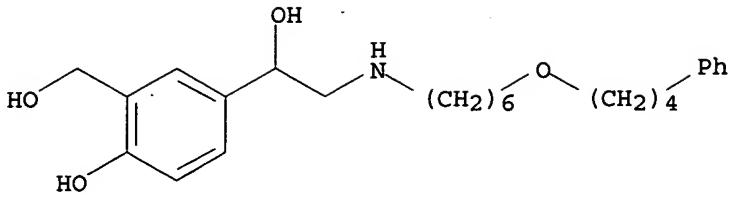
L8 ANSWER 86 OF 255 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:287785 CAPLUS
DOCUMENT NUMBER: 140:315099
TITLE: A combination of a long-acting β 2-agonist and a glucocorticosteroid in the treatment of fibrotic diseases
INVENTOR(S): Trofast, Jan; Westergren-Thorsson, Gunilla
PATENT ASSIGNEE(S): Astrazeneca AB, Swed.
SOURCE: PCT Int. Appl., 24 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004028545	A1	20040408	WO 2003-SE1486	20030924
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2003263717	A1	20040419	AU 2003-263717	20030924
PRIORITY APPLN. INFO.:			SE 2002-2837 A	20020925
			SE 2003-106 A	20030116
			WO 2003-SE1486 W	20030924

AB The invention discloses the use of glucocorticosteroids and long-acting beta.2-agonists in the treatment of various fibrotic diseases, e.g. idiopathic pulmonary fibrosis, allergic alveolitis, and cystic fibrosis. The preferred combination of active substances consists of budesonide and formoterol fumarate dihydrate.

IT 89365-50-4, Salmeterol 94749-08-3, Salmeterol xinafoate 452339-68-3 463934-65-8
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(long-acting β 2-agonist -glucocorticosteroid combination for treatment of fibrotic disease)

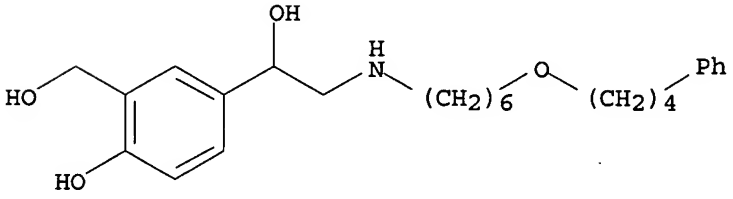
RN 89365-50-4 CAPLUS
CN 1,3-Benzenedimethanol, 4-hydroxy-α1-[[[6-(4-phenylbutoxy)hexyl]amino]methyl]- (9CI) (CA INDEX NAME)



RN 94749-08-3 CAPLUS
CN 2-Naphthalenecarboxylic acid, 1-hydroxy-, compd. with 4-hydroxy-α1-[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-1,3-benzenedimethanol (1:1) (9CI) (CA INDEX NAME)

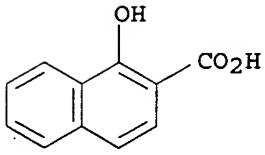
CM 1

CRN 89365-50-4
CMF C25 H37 N O4



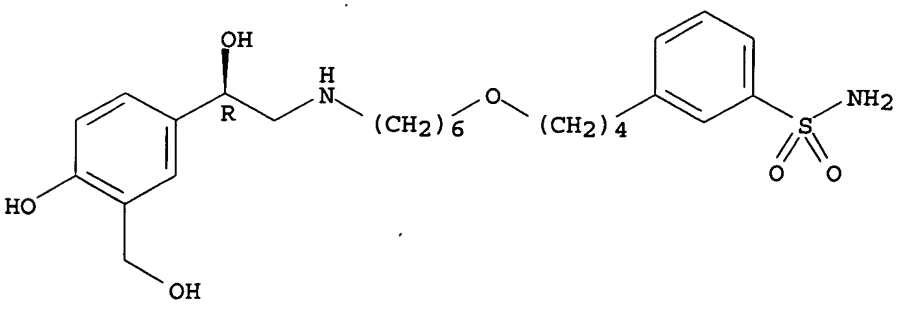
CM 2

CRN 86-48-6
CMF C11 H8 O3



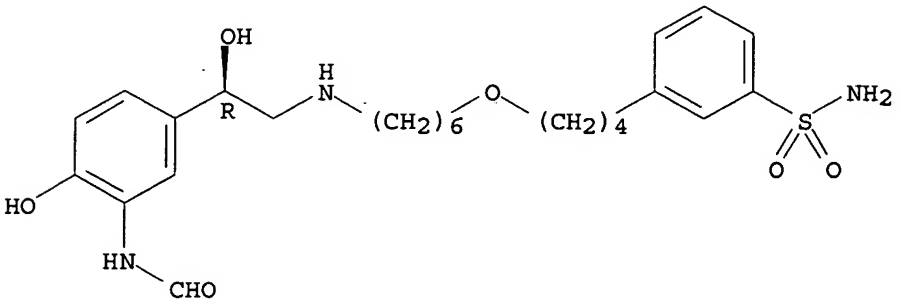
RN 452339-68-3 CAPLUS
CN Benzenesulfonamide, 3-[4-[[6-[[(2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino]hexyl]oxy]butyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 463934-65-8 CAPLUS
CN Benzenesulfonamide, 3-[4-[[6-[[(2R)-2-[3-(formylamino)-4-hydroxyphenyl]-2-hydroxyethyl]amino]hexyl]oxy]butyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 87 OF 255 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:273878 CAPLUS
DOCUMENT NUMBER: 141:271723
TITLE: Corticosteroids and β2-adrenergic agonists differentially modulate the synthesis and secretion of glycosaminoglycans by human lung cells
AUTHOR(S): Papakonstantinou, E.; Roth, M.; Tamm, M.; Karakiulakis, G.
CORPORATE SOURCE: Dept Pharmacology, School of Medicine, Aristotle University, Thessaloniki, 54124, Greece
SOURCE: Epitheorese Klinikes Farmakologias kai Farmakokinetikes, International Edition (2004), 18(1), 156-160
CODEN: EFKEEB; ISSN: 1011-6583
PUBLISHER: Pharmakon-Press
DOCUMENT TYPE: Journal
LANGUAGE: English

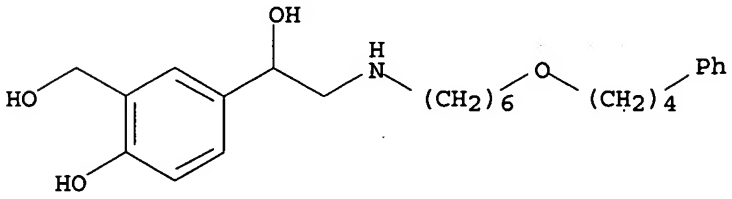
AB Asthma is characterized by airway remodeling, involving changes in deposition of extracellular matrix mols. First-line therapy of persistent asthma involves the combination of inhaled corticosteroids and β2 adrenergic agonists. The aim of this study was to investigate the effect of corticosteroids, .beta.2 agonists and their combination in the secretion and deposition of glycosaminoglycans (GAGs) by human lung cells. Human bronchial epithelial and smooth muscle cells and lung fibroblasts were incubated for 48 h in the presence of budesonide, ciclesonide, formoterol or salmeterol. GAGs were determined in the cell culture medium and in the cell-associated matrix by 3H-glucosamine incorporation. We found that budesonide and ciclesonide resulted in a dose-dependent decrease in both cell-associated and secreted GAGs to approx. 50% of control levels. This effect was inhibited by the corticosteroid antagonist mifepristone, indicating the involvement of corticosteroid receptors. Formoterol and salmeterol had no effect. However, the combination of .beta.2 agonists with corticosteroids further enhanced the inhibitory effect of corticosteroids. This effect was mediated via adrenergic receptors since it was abolished by propranolol. These results demonstrate that the anti-inflammatory action of corticosteroids when used alone or in combination with β2 adrenergic agonists in the treatment of asthma may also be associated with a beneficiary decrease in the deposition of matrix mols. in the lung.

IT 89365-50-4, Salmeterol

(Uses)
(influence of receptor number on the stimulation by salmeterol of gene transcription in CHO-K1 cells transfected with the human β2-adrenoceptor)

RN 89365-50-4 CAPLUS

CN 1,3-Benzenedimethanol, 4-hydroxy-α1-[[[6-(4-phenylbutoxy)hexyl]amino]methyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 193 OF 255 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1998:719273 CAPLUS
DOCUMENT NUMBER: 129:342949
TITLE: Composition and methods using an eutomer
INVENTOR(S): Aberg, A. K. Gunnar; Fawcett, J. Paul
PATENT ASSIGNEE(S): Bridge Pharma, Inc., USA
SOURCE: PCT Int. Appl., 16 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9848810	A1	19981105	WO 1998-US8611	19980429
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2286913	A1	19981105	CA 1998-2286913	19980429
AU 9872650	A	19981124	AU 1998-72650	19980429
AU 737608	B2	20010823		
EP 979081	A1	20000216	EP 1998-919978	19980429
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
US 6110974	A	20000829	US 1998-69512	19980429
NZ 500250	A	20010330	NZ 1998-500250	19980429
BR 9815470	A	20011023	BR 1998-15470	19980429
JP 2001527545	T	20011225	JP 1998-547320	19980429
MX 9909783	A	20000731	MX 1999-9783	19991025
NO 9905308	A	19991221	NO 1999-5308	19991029

PRIORITY APPLN. INFO.:
US 1997-45120P P 19970430
WO 1998-US8611 W 19980429

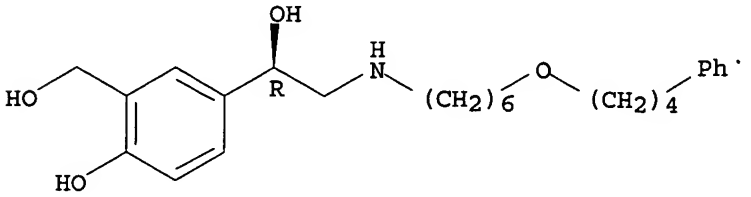
AB Method for improving health, survival and muscle growth rate of animals, while reducing carcass fat and improving feed efficiency by administering an optically pure eutomer of an adrenergic beta-2 agonist. The invention is also directed to food compns.

comprising the adrenergic beta-2 agonists.

IT 135271-47-5, R-Salmeterol 135271-48-6, S-Salmeterol
RL: AGR (Agricultural use); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(composition and methods for feeding animals using an eutomer)

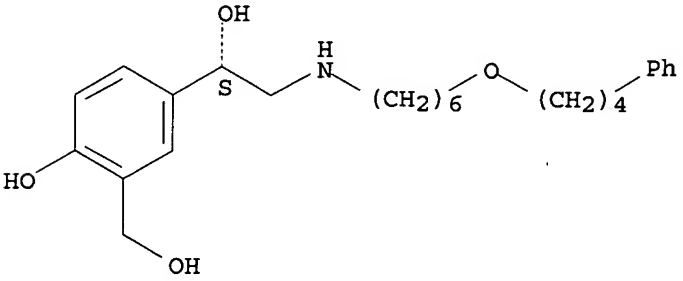
RN 135271-47-5 CAPLUS
CN 1,3-Benzenedimethanol, 4-hydroxy-α1-[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-, (α1R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RN 135271-48-6 CAPLUS
CN 1,3-Benzenedimethanol, 4-hydroxy-α1-[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-, (α1S)- (9CI) (CA INDEX NAME)

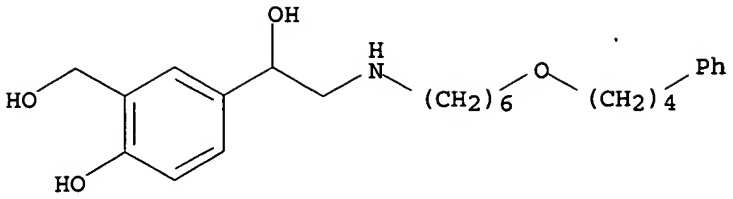
Absolute stereochemistry.



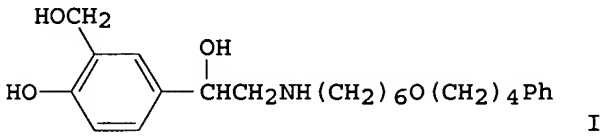
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 194 OF 255 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1998:703346 CAPLUS
DOCUMENT NUMBER: 130:105080
TITLE: Effects of β2 adrenoceptor agonists on T-cell subpopulations
AUTHOR(S): Holen, E.; Elsayed, S.
CORPORATE SOURCE: Allergy Research Group, Department of Clinical Biochemistry, University Hospital, Bergen, Norway
SOURCE: APMIS (1998), 106(9), 849-857
CODEN: APMSEL; ISSN: 0903-4641
PUBLISHER: Munksgaard International Publishers Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The aim of the present communication is to determine the effects of β2 adrenoceptor agonists on growth and cytokine secretion using allergen-specific T cells. Four β2 adrenoceptor agonists were administered at therapeutically relevant doses (salbutamol 1-2 μM; salmeterol 0.03-0.06 μM; terbutaline 0.56-1.12 μM, and fenoterol 0.7-1.4 μM) to: (a) Cultures of human peripheral mononuclear cells (PBMC); (b) Pos. selected CD4+ and CD8+ subsets; (c) Allergen-specific T-cell lines (TCL). Drug effects on growth kinetics and the secretion of

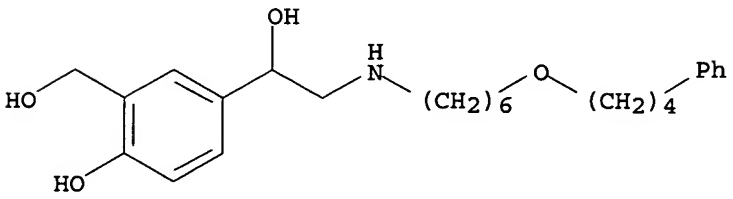


L8 ANSWER 246 OF 255 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1994:152724 CAPLUS
DOCUMENT NUMBER: 120:152724
TITLE: Salmeterol: a novel, long-acting beta2-agonist
AUTHOR(S): Meyer, Joette M.; Wenzel, Christine L.; Kradjan, Wayne A.
CORPORATE SOURCE: Coll. Pharm., Univ. Illinois, Chicago, IL, 60680, USA
SOURCE: Annals of Pharmacotherapy (1993), 27(12), 1478-87
CODEN: APHRER; ISSN: 1060-0280
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
GI



I

AB A review with 61 refs. Salmeterol (I) is an effective β 2-agonist in the treatment of asthma. However, several issues require further investigation regarding its long-term effects on disease control, significance of anti-inflammatory activity, and role as a rescue medication.
IT 89365-50-4, Salmeterol
RL: BIOL (Biological study)
(as long-acting β 2-agonist)
RN 89365-50-4 CAPLUS
CN 1,3-Benzenedimethanol, 4-hydroxy-α1-[[[6-(4-phenylbutoxy)hexyl]amino]methyl]- (9CI) (CA INDEX NAME)



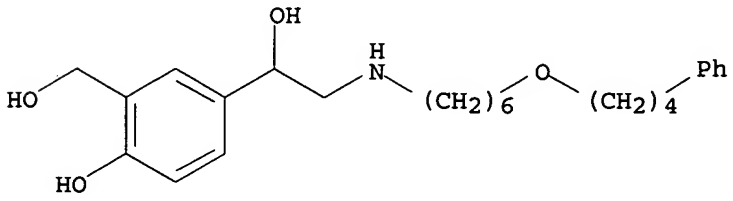
L8 ANSWER 247 OF 255 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1993:595441 CAPLUS
DOCUMENT NUMBER: 119:195441
TITLE: Effect on airway responsiveness of six weeks treatment with salmeterol

AUTHOR(S): Beach, J. R.; Young, C. L.; Harkawat, R.; Gardiner, P. V.; Avery, A. J.; Coward, G. A.; Walters, E. H.; Hendrick, D. J.
CORPORATE SOURCE: Chest Unit, Newcastle Gen. Hosp., Newcastle upon Tyne, NE4 6BE, UK
SOURCE: Pulmonary Pharmacology (1993), 6(2), 155-7
CODEN: PUPHEX; ISSN: 0952-0600
DOCUMENT TYPE: Journal
LANGUAGE: English

AB It has been suggested that the new long-acting .beta.2 -agonist, salmeterol, has anti-inflammatory properties- properties which should improve airway responsiveness (AR). Conversely, several recent studies have suggested that regular β 2-agonist treatment may worsen asthma and AR. Furthermore, a short-lived rebound increase in AR has been described following cessation of regular treatment with these agents. The authors have consequently assessed the effects on AR of regular treatment with either salmeterol or salbutamol at conventional doses over 6 wk. FEV1 and AR were measured five times in 20 asthmatic subjects randomly allocated to one or other treatment regimen; twice during a 2-wk run-in period; and 24 h, 72 h, and 2 wk after the last dose of the study medication. Peak expiratory flow rate (PEFR) was also recorded throughout the study period. There were no statistically significant changes in FEV1 or AR between the run-in period and any of the post treatment measurements for either of the treatments used. Mean PEFR was significantly higher during the treatment period than the run-in period for the salmeterol group, but not the salbutamol group, confirming that therapeutically adequate doses of salmeterol had been given. The authors conclude that if the regular use of salmeterol is associated with beneficial or adverse effects on AR, this is not apparent after a treatment period of 6 wk.

IT 89365-50-4, Salmeterol
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(antiasthmatic activity of, in humans)

RN 89365-50-4 CAPLUS
CN 1,3-Benzenedimethanol, 4-hydroxy-α1-[[[6-(4-phenylbutoxy)hexyl]amino]methyl]- (9CI) (CA INDEX NAME)



L8 ANSWER 248 OF 255 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1993:462266 CAPLUS
DOCUMENT NUMBER: 119:62266
TITLE: The pharmacology of salmeterol
AUTHOR(S): Johnson, M.; Butchers, P. R.; Coleman, R. A.; Nials, A. T.; Strong, P.; Summer, M. J.; Vardey, C. J.; Whelan, C. J.
CORPORATE SOURCE: Dep. Cardiovasc. Respir. Pharmacol., Glaxo Group Res. Ltd., Ware/Hertfordshire, UK
SOURCE: Life Sciences (1993), 52(26), 2131-43
CODEN: LIFSAK; ISSN: 0024-3205
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

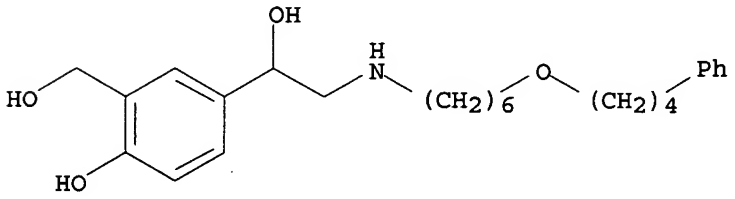
AB A review with 45 refs. Salmeterol was developed to provide prolonged

bronchodilation to control nocturnal symptoms and improve maintenance therapy in asthmatic patients. Salmeterol is > 10,000 times more lipophilic than salbutamol and has greater affinity for the β2-adrenoceptor. Membrane binding is non-competitive and dissociation is slow so that its effects last for many hours. Despite this, salmeterol does not accumulate in tissues. Its mechanism of action can be explained by binding to a specific exo-site domain of the β2-adrenoceptor. Membrane binding is non-competitive and dissociation is slow so that its effects last for many hours. Despite this, salmeterol does not accumulate in tissues. Its mechanism of action can be explained by binding to a specific exo-site domain of the β2-receptor protein to produce continuous stimulation of the active site of the receptor, which gives salmeterol a profile of pharmacol. activity unlike that of other . beta.2-agonists. Due to its potent and prolonged activation of β2-adrenoceptors in airway smooth muscle cells, endothelial cells, mast cells and epithelial cells, salmeterol induces prolonged bronchodilation, reduced vascular permeability, inhibition of inflammatory mediators, stimulation of ciliary function and modulation of ion and water transport across the bronchial mucosa.

IT 89365-50-4, Salmeterol
RL: BIOL (Biological study)
(as antiasthmatic, pharmacol. of)

RN 89365-50-4 CAPLUS

CN 1,3-Benzenedimethanol, 4-hydroxy-α1-[[[6-(4-phenylbutoxy)hexyl]amino]methyl]- (9CI) (CA INDEX NAME)



L8 ANSWER 249 OF 255 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1993:247326 CAPLUS

DOCUMENT NUMBER: 118:247326

TITLE: Investigations into factors determining the duration of action of the β2-adrenoceptor agonist, salmeterol

AUTHOR(S): Nials, Anthony T.; Sumner, Michael J.; Johnson, Malcolm; Coleman, Robert A.

CORPORATE SOURCE: Dep. Cardiovasc. Respiratory Pharmacol., Glaxo Group Res., Ware/Hertfordshire, SG12 0DP, UK

SOURCE: British Journal of Pharmacology (1993), 108(2), 507-15
CODEN: BJPCBM; ISSN: 0007-1188

DOCUMENT TYPE: Journal

LANGUAGE: English

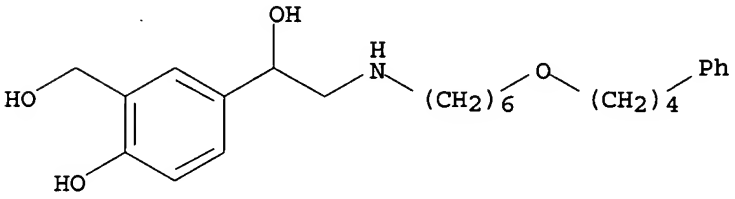
AB This study has explored the mechanism underlying the long duration of action of the β2-adrenoceptor agonist, salmeterol. Salmeterol, salbutamol and isoprenaline caused a concentration-related inhibition of elec.-induced contractile responses of the guinea-pig superfused trachea preparation The effects of both isoprenaline and salbutamol were rapid in onset and rapidly reversed upon removal of the agonist. In contrast, the effects of salmeterol were slower in onset and could not be reversed by superfusion of the tissue with agonist-free Krebs solution even for periods of up to 10 h. The effects of salmeterol were, however, readily reversed by a number of β-adrenoceptor blocking drugs, as was the effect of a continuous infusion of isoprenaline. Upon removal of the antagonist, however, the effects of salmeterol and of the isoprenaline infusion were

reasserted at a rate which was inversely related to the lipophilicity of the β-adrenoceptor blocking drugs. Salmeterol inhibited the binding of [125I]-(-)-iodopindolol (100 pM) to rat lung membranes (pIC50. 7.1), with isoprenaline (pIC50 6.2) and salbutamol (pIC50 5.1) having lower potencies. The inhibition of binding by salmeterol was apparently non-competitive, whereas that produced by salbutamol and isoprenaline was competitive in nature. Isoprenaline and salbutamol rapidly dissociated from their binding sites, whereas in marked contrast, the binding of salmeterol showed no dissociation for periods of up to 1 h. These data are consistent with a mechanism in which salmeterol binds adjacent to the active site of the β2-adrenoceptor, such that the drug cannot be washed out of the tissue, yet can interact with and activate the receptor. This latter property is susceptible to antagonism by β-adrenoceptor blocking drugs but is reasserted when the antagonists are removed.

IT 89365-50-4, Salmeterol
RL: BIOL (Biological study)
(as β2-adrenergic agonist in lung membrane and trachea, binding in relation to duration of action of)

RN 89365-50-4 CAPLUS

CN 1,3-Benzenedimethanol, 4-hydroxy-α1-[[[6-(4-phenylbutoxy)hexyl]amino]methyl]- (9CI) (CA INDEX NAME)



L8 ANSWER 250 OF 255 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1993:32526 CAPLUS

DOCUMENT NUMBER: 118:32526

TITLE: Equilibrium and kinetic studies of the interactions of salmeterol with membrane bilayers

AUTHOR(S): Rhodes, David G.; Newton, Roger; Butler, Rondi; Herbette, Leo

CORPORATE SOURCE: Biomol. Struct. Anal. Cent., Univ. Connecticut, Farmington, CT, 06030-2017, USA

SOURCE: Molecular Pharmacology (1992), 42(4), 596-602
CODEN: MOPMA3; ISSN: 0026-895X

DOCUMENT TYPE: Journal

LANGUAGE: English

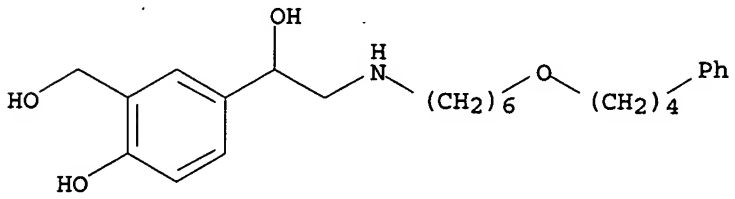
AB The interaction of salmeterol with model membranes has been studied with regard to equilibrium and kinetic behavior, including determination of the membrane-based partition coefficient, the rate of dissociation of salmeterol from membranes, and the rate of association These data were obtained in various membrane prepns. and under various conditions (e.g., temperature, cholesterol content). The compound is very lipophilic, compared with other . beta.2 agonists such as salbutamol, and has a rapid association rate and a moderate dissociation rate. The equilibrium data support the assertion that the salmeterol action measured in perfused tissue involves an exo-site for nonspecific binding that may be identified with or related to the lipid bilayer. The kinetic data in unilamellar and multilamellar liposomes of synthetic lipids further suggest that the approach to the exo-site and the active site may involve components in the native system other than the lipid bilayer in which the β2 receptor is located. These addnl. components may explain the slow onset and the

extraordinarily long duration of action.

IT 89365-50-4, Salmeterol
RL: BIOL (Biological study)
(interaction with lipid bilayer membranes, slow onset and duration of action and structure in relation to)

RN 89365-50-4 CAPLUS

CN 1,3-Benzenedimethanol, 4-hydroxy-α1-[[[6-(4-phenylbutoxy)hexyl]amino]methyl]- (9CI) (CA INDEX NAME)



L8 ANSWER 251 OF 255 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1992:645324 CAPLUS

DOCUMENT NUMBER: 117:245324

TITLE: Onset of action and duration of effect of formoterol and salmeterol compared to salbutamol in isolated guinea pig trachea with or without epithelium

AUTHOR(S): Ullman, A.; Bergendal, A.; Linden, A.; Waldeck, B.; Skoogh, B. E.; Loefdahl, C. G.

CORPORATE SOURCE: Dep. Clin. Pharmacol., Sahlgren's Hosp., Goeteborg, S-411 23, Swed.

SOURCE: Allergy (Oxford, United Kingdom) (1992), 47(4, Pt. 2), 384-7
CODEN: LLRGDY; ISSN: 0105-4538

DOCUMENT TYPE: Journal

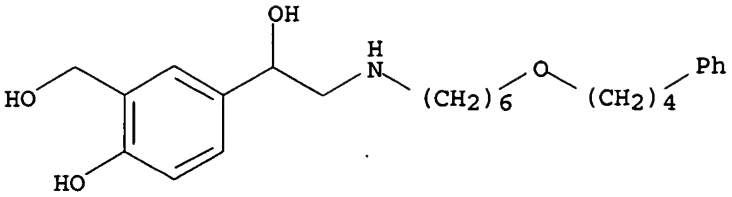
LANGUAGE: English

AB Formoterol and salmeterol are 2 newly developed β2-adrenoceptor agonists for inhalation with prolonged duration of effect compared with currently available .beta.2-agonists. The clin. duration of effect has been suggested to be correlated to a decreased washability in vitro, i.e. decreased effect due to continuous washing of the organ bath. In this study, the authors compared the washability and the onset of the relaxatory effect of formoterol (0.01 μM), salmeterol (0.05 μM) and salbutamol (0.1 μM) in isolated guinea pig trachea contracted with carbachol (0.1 μM). The authors also evaluated a possible influence of the epithelium on onset of action and/or duration of effect. A significant relaxatory effect of formoterol and salmeterol remained after washing, whereas no effect of salbutamol remained. The authors also found a rapid onset of action for both salbutamol and formoterol, but a significantly slower onset for salmeterol. Both the washability and the onset of action were found to be independent of the presence of the epithelium. This study confirms the clin. data indicating a prolonged bronchorelaxant effect of salmeterol and formoterol, and shows that this effect does not depend on an intact epithelium.

IT 89365-50-4
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(bronchodilator activity of, epithelium in)

RN 89365-50-4 CAPLUS

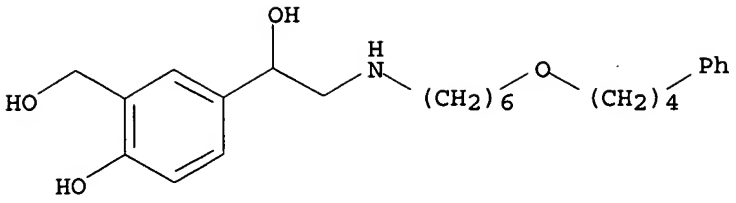
CN 1,3-Benzenedimethanol, 4-hydroxy-α1-[[[6-(4-phenylbutoxy)hexyl]amino]methyl]- (9CI) (CA INDEX NAME)



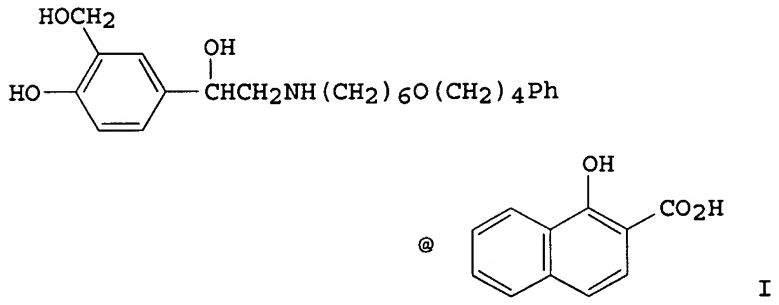
L8 ANSWER 252 OF 255 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1992:564584 CAPLUS
DOCUMENT NUMBER: 117:164584
TITLE: The effects of β2-adrenoceptor agonists and a corticosteroid, budesonide, on the secretion of inflammatory mediators from monocytes
AUTHOR(S): Linden, Margareta
CORPORATE SOURCE: Pharmacol. 1. Res. Dev. Dep., Astra Draco AB, Lund, S-221 00, Swed.
SOURCE: British Journal of Pharmacology (1992), 107(1), 156-60
CODEN: BJPCBM; ISSN: 0007-1188
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The in vitro effects of the β2-adrenoceptor agonists (1 + 10-9-10-5 M), terbutaline, salmeterol, and formoterol on the release of inflammatory mediators, i.e. the eicosanoids LTB4 and PGE2 and the cytokine interleukin-1β (IL-1β), were assessed in cultures of human blood monocytes. For comparison, the effects of a 5-lipoxygenase inhibitor, BW A4C (1 + 10-9-10-5 M), and a corticosteroid, budesonide (1 + 10-10-10-5 M) were also examined Sotalol was used to investigate whether the actions of .beta.2-agonists were mediated through β-adrenoceptors. Terbutaline, like budesonide, had no significant effect on LTB4 release, whereas BW A4C (IC50 = 2 + 1--8 M) was a potent inhibitor. All concns. of formoterol approx. halved the LTB4 secretion, whereas only high concns. (1 + 10 -7-10-5M) of salmeterol inhibited release. Only salmeterol, at high concns. (>1 + 10-8 M), lowered the secretion of PGE2 in monocyte cultures. Formoterol and salmeterol reduced the secretion of IL-1β only at the highest dose (1 + 10-5 M). In contrast, budesonide (≥1 + 10-9 M) was a potent suppressant of this secretion. Treatment of monocyte cultures with sotalol (1 + 10-5 M) did not antagonize the inhibitory effects of salmeterol and formoterol. These results suggest that the inhibitory action of these β 2-agonists on the release of eicosanoids or IL-1β is not mediated via β2-adrenoceptors. This study does not support a therapeutic importance of the anti-release effects of β 2-agonists since high concns. were generally required. Furthermore, the anti-secretory action of .beta.2-agonists was distinct from that of corticosteroids.

IT 89365-50-4, Salmeterol
RL: BIOL (Biological study)
(inflammatory mediators release by monocytes from human response to)
RN 89365-50-4 CAPLUS
CN 1,3-Benzenedimethanol, 4-hydroxy-α1-[[[6-(4-phenylbutoxy)hexyl]amino]methyl]- (9CI) (CA INDEX NAME)



L8 ANSWER 253 OF 255 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1991:526862 CAPLUS
DOCUMENT NUMBER: 115:126862
TITLE: Pharmacological action of SN 408, a novel long-acting selective β2-adrenoceptor agonist
AUTHOR(S): Nishimura, Makoto; Okiyama, Masahiko; Fujiwara, Hajime; Kudo, Mariko; Simizu, Mayumi; Maeda, Mariko; Yamada, Mayumi; Toshimitsu, Yoshinobu
CORPORATE SOURCE: Tokyo Res. Lab., Nippon Glaxo Ltd., Tokyo, 177, Japan
SOURCE: Nippon Yakurigaku Zasshi (1991), 98(1), 7-21
CODEN: NYKZAU; ISSN: 0015-5691
DOCUMENT TYPE: Journal
LANGUAGE: Japanese
GI

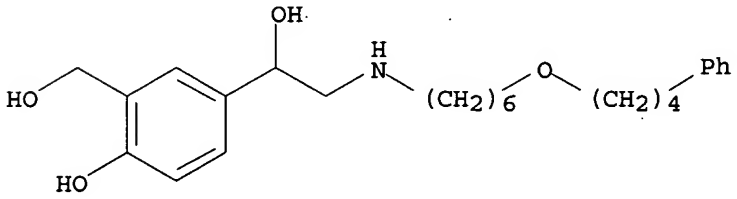


AB The bronchodilating effect and other related pharmacol. properties of SN 408 (I) were studied in comparison with those of isoproterenol, salbutamol and procaterol. SN 408 caused concentration-dependent relaxation of isolated guinea pig trachea via the β2-adrenoceptor. The order of relaxation potency was: procaterol > SN 408 ≥ isoproterenol > salbutamol, but the duration of the action of SN 408 was far longer than those of other β-agonists. Pos. chronotropic and inotropic actions of SN 408 in isolated guinea pig right atria and left atria were less potent than those of other β-agonists. In isolated guinea pig lung tissues, SN 408 increased cAMP contents. Also in vivo, SN 408 showed dose-dependent bronchodilating action by i.v. administration in anesthetized guinea pigs and by inhalation in conscious guinea pigs. Bronchodilating actions of SN 408 were less potent than those of procaterol and isoproterenol, but the duration of action of SN 408 was far longer than those of other β-agonists. SN 408 showed no evidence of the development of tolerance to the bronchodilating action. SN 408 caused small tachycardia in guinea pigs by i.v. and inhalation. SN 408 given i.v. suppressed vascular permeability in mice. Thus, SN 408 is a long-acting and selective β2-stimulant bronchodilator.
IT 94749-08-3, SN 408

RL: BIOL (Biological study)
(bronchodilating β 2-agonist,
pharmacol. of)
RN 94749-08-3 CAPLUS
CN 2-Naphthalenecarboxylic acid, 1-hydroxy-, compd. with 4-hydroxy-α1-[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-1,3-benzenedimethanol (1:1) (9CI) (CA INDEX NAME)

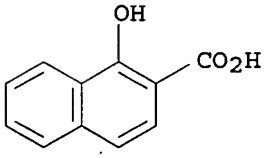
CM 1

CRN 89365-50-4
CMF C25 H37 N O4



CM 2

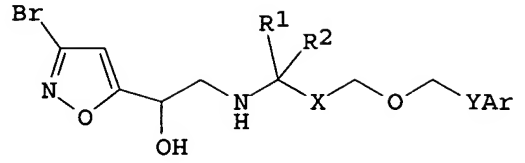
CRN 86-48-6
CMF C11 H8 O3



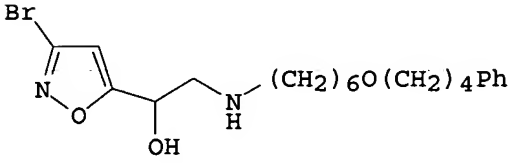
L8 ANSWER 254 OF 255 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1991:143404 CAPLUS
DOCUMENT NUMBER: 114:143404
TITLE: Preparation of 1-(3-bromoisoxazol-5-yl)-2-aminoethanol derivatives as .beta.2 agonists
INVENTOR(S): Bradshaw, John; Lunts, Lawrence Henry Charles
PATENT ASSIGNEE(S): Glaxo Group Ltd., UK
SOURCE: Brit. UK Pat. Appl., 14 pp.
CODEN: BAXXDU
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
GB 2230523	A	19901024	GB 1989-8466	19890414

PRIORITY APPLN. INFO.: GB 1989-8466 19890414
OTHER SOURCE(S): MARPAT 114:143404
GI



I



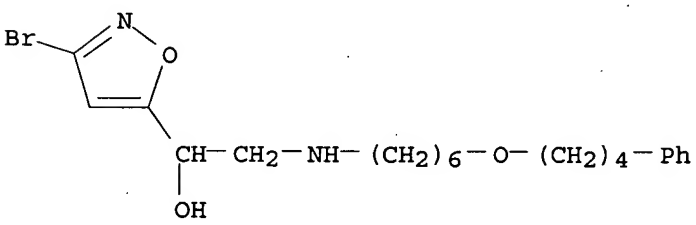
II

AB The title compds. [I; R1, R2 = H, alkyl; X, Y = bond, alkylene, alkenylene, alkynylene; Ar = (substituted) Ph, pyridyl], were prepared as β2 adrenoceptor stimulants for treatment of asthma, bronchitis, inflammatory/allergic skin disorders, congestive heart failure, depression, premature labor, glaucoma, and gastric/peptic ulceration (no data). Thus, a mixture of 1-(3-bromoisoxazol-5-yl)-2-bromoethanol, 6-(4-phenylbutoxy)hexanamine, and (Me2CH)2NEt was refluxed 14 h in EtOH to give title compound II.

IT 132808-25-4P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, as β 2 agonist)

RN 132808-25-4 CAPLUS

CN 5-Isoxazolemethanol, 3-bromo-α-[[[6-(4-phenylbutoxy)hexyl]amino]methyl]- (9CI) (CA INDEX NAME)



L8 ANSWER 255 OF 255 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1991:16941 CAPLUS

DOCUMENT NUMBER: 114:16941

TITLE: Long-term studies on long-acting sympathomimetics

AUTHOR(S): Larsson, Sven

CORPORATE SOURCE: Dep. Pulmonary Med., Goeteborg Univ., Goeteborg, Swed.

SOURCE: Lung (1990), 168(Suppl.), 22-4
CODEN: LUNGD9; ISSN: 0341-2040

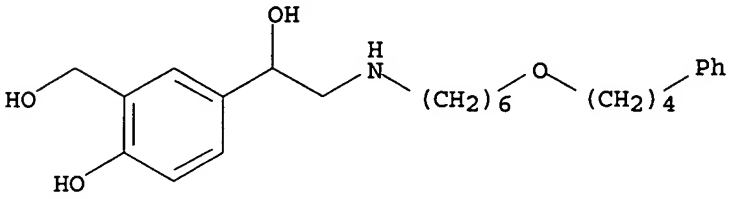
DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review with 3 refs. Long-term treatment studies with formoterol and salmeterol show that these inhaled long-acting .beta.2 -agonists compared to available .beta.2-agonists produce better bronchodilation, decrease the need for addnl. doses, decrease asthma symptoms, and are strongly preferred by the patients. Development of tolerance has not been found. One case history indicates that these effective bronchodilators might mask deterioration of asthma.

IT 89365-50-4, Salmeterol

RL: BIOL (Biological study)
(in treatment of asthma)
RN 89365-50-4 CAPLUS
CN 1,3-Benzenedimethanol, 4-hydroxy-α1-[[[6-(4-phenylbutoxy)hexyl]amino]methyl]- (9CI) (CA INDEX NAME)



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L3 800 S L1 FULL

FILE 'CAPLUS' ENTERED AT 10:47:17 ON 13 MAR 2007
L4 1209 S L3
L5 924 S L3/THU
L6 5 S ADRENERGIC BETA2 AGONIST?
L7 1731 S BETA 2 AGONIST?
L8 255 S L4 AND L7

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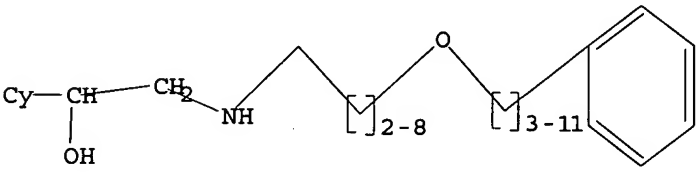
L1 HAS NO ANSWERS
L1 STR



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